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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/012,194	12/06/2001	Manuela Martins-Green	407E-914500US	5287

22798 7590 05/24/2006

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/012,194	MARTINS-GREEN ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-6,9-15,18-20,23,25,26,43,44 and 46-48* is/are pending in the application.

4a) Of the above claim(s) *2-6,9-15,18-20,23,25,26,43,44 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47 and 48* is/are rejected.

7)☒ Claim(s) *47 and 48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 August 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-6, 9-15, 18-20, 23, 25, 26, 43, 44, 46-48 are pending in the application.

This Office Action is in response to the Amendment filed on 3/6/06.

Response to Amendment

Claims 47 and 48 stand rejected under 35 U.S.C.103 (a) for reasons set forth of the record mailed on 11/2/05 and further discussed below.

Claims 47 and 48 are objected to for reason given below.

Claim 48 is rejected under 35 U.S.C. 112 1st paragraph for reasons given below.

Election/Restrictions

Newly submitted claims 2-6, 9-15, 18-20, 23, 25, 26, 43, 44 and 46, directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The newly amended claims are drawn to a method of making an artificial tissue, which belongs to the invention of Group II as set forth in the restriction requirement mailed on 8/26/03. The method is patentably distinct from the product made because the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, the artificial tissue of Group I (2-6, 9-15, 18-20, 23, 25, 26, 43, 44, as presented previously) can also be made by other methods, for example, culturing progenitor cells in cytokines and growth factors that regulate the differentiation of these cells into proper tissue. Therefore, the presently amended method claims are patentably distinct from the product claims presented before.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 2-6, 9-15, 18-20, 23, 25, 26, 43, 44 and newly added claim

46 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Accordingly, claims 47 and 48 are currently under examination.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Response to Arguments

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Black et al., in view of Fransson et al (British Joumal of Dermatology, 1998,Vol 139: pages 59-604) and Montesano et al.

Black et al. teach a skin equivalent preparation comprising human keratinocytes plated on endothelial dermal equivalent or endothelial fibroblast dermal equivalent mixed with collagen (see page 1333, 1st col., 2nd and 3rd paragraph). Black et al. also teach that the endothelial fibroblast dermal equivalent comprising fibroblast and HUVEC (see page 1333, 1st col., 2nd paragraph). Black et al. further teach that a network of capillary-like tubular structures is formed in the tissue (see page 1333, 2nd col., 3rd and 5th paragraph). Furthermore, Black et al. teach that said tissue produces laminin, type IV collagen and extracellular matrix (see page 1334, 1st col., 2nd paragraph, and Figures 1, 2 and 3). Moreover, Black et al. disclose that said tissue is self maintained *in vitro*, and is suitable for tissue graft (see page 1338, entire 1st col., and 2nd col., 2nd paragraph).

However, Black et al. do not teach an artificial tissue comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells. Black et al. do not teach said microvessel that produces mononuclear leukocytes.

Montesano et al. teach endothelial cell monolayers established on the surface of collagen matrix and covered with another layer of collagen matrix induces the endothelial cells to

reorganize into a network of branching and anastomosing capillary-like tubes resembling capillary beds *in vivo* (see page 1649, 2nd col., 3rd paragraph, lines 1-4). Montesano et al. further teach that an appropriate topological relationship of endothelial cells with collagen matrices, similar to that occurring in vivo, has an inductive role for endothelial cells to form vessel-like structures *in vitro* (see abstract).

Fransson et al. teach that a *in vitro* cultured skin equivalent that comprises mononuclear leukocytes which expresses CD 86 and CD 80 (seepage 603, 1st col., 1st paragraph).

It would have been obvious to one of ordinary skill in the art to make an artificial skin equivalent as taught by Black et al. and introduce a second layer of connective tissue on top of the endothelial cell based on the teaching of Montesano et al. One of ordinary skill in the art would have been motivated to do so because it would resemble the capillary bed *in vivo* and thus induce capillary formation closely resemble that of *in vivo* setting, as demonstrated by Montesano et al. The ordinary artisan would also have been motivated to add LC cells to the culture so that the immature antigen presenting cells can be produced and the skin equivalent can be used as an allergy model. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to make the tissue as claimed. Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants assert that Black et al. do not teach the claim limitation of "mixing together a support matrix and connective tissue cells to form a support matrix-connective tissue mixture" because it only teaches seeding fibroblast, endothelial cells on top of the biopolymer. Applicants further assert that Montesano et al. do not teach mixing a collagen solution with an entirely

different cell type such as the connective tissue cells. Moreover, Applicants argue there is no rationale for why one of skill in the art would extrapolate any findings from a dermal equivalent as taught by Fransson et al. to cultures consisting of one to three cell types and a support matrix. Applicants assert that the method of Fransson et al. is too different from the methods described by Black and Montesano to teach or suggest anything about whether such cultures could produce mononuclear leukocytes. Furthermore, Applicants argue that the cited references teaches systems for different use, thus there is no motivation to combine the references according to *In re Rouffet* and *In re Kotzab.* Applicants thus conclude that the claimed invention is not obvious in view of the cited references.

The above argument has been fully considered but deemed unpersuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to Applicant's argument with regard to the mixture of matrix and connective tissue, Applicants are reminded that this limitation does not exclude plating the cell on top of a matrix in a plate because it also forms a mixture. The specification does not define "mixture" as being in a particular form. Thus, the cited reference does meet this limitation.

In response to Applicants' argument that Fransson et al. is too different from the methods described by Black and Montesano, Applicants are reminded that this reference is certainly considered as analogous art because it also teaches dermal equivalent, which would be used for artificial tissue regardless how the dermal equivalent is made. The teaching that a *in vitro*

cultured skin equivalent that comprises mononuclear leukocytes which expresses CD 86 and CD 80 (seepage 603, 1st col., 1st paragraph) by Fransson not only gives motivation, to make a dermal equivalent as closely resembles a real dermal tissue, also gives guidance and reasonable expectation of success for how to produce mononuclear leukocytes in such an artificial tissue. Applicants are reminded that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teaching of Black, Montesano, and Fransson et al gives sufficient motivation to combine the references and reach the claimed invention. Therefore, for reasons given in the previous office action and above, this rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Objections

Claims 47 and 48 are objected to for depending on non-elected claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 48 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 48 depends on newly added claim 46. Although claim 46 is withdrawn from consideration, the limitation of claim 46 is read into claim 48 to expedite the prosecution.

Claim 46, thus also the dependent claim 48, recites the limitation of "wherein microvessels and mononuclear leukocytes are not present in the original culture, but are formed during culturing." This limitation is not supported by the original filed specification. Although in the example given in the specification the microvessels and mononuclear leukocytes are formed during culturing, it does not fully support any artificial tissue has leukocytes and microvessels formed during the culture. Therefore, such recitation constitutes new matter.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELINE QIAN, PH.D.
PRIMARY EXAMINER